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A randomized controlled study of patients with non-small-cell lung cancer administered Ramucirumab with Docetaxel complying with combination of chemotherapy

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A B S T R A C T

Background: It has been noted that positive results from ramucirumab (RAM) plus docetaxel (DOC) combination therapy for advanced non-small-cell lung cancer (NSCLC) are linked to a history of immune checkpoint inhibitor pre-administration. Nevertheless, nothing is now known about the therapeutic importance of RAM and DOC after combined chemoimmunotherapy. Thus, following combination chemoimmunotherapy, we assessed the safety and effectiveness of RAM + DOC therapy and tried to determine the factors that might influence its results.

Patients and Methods: Following combination chemotherapy and immunotherapy, this multi-center prospective trial examined the safety and effectiveness of RAM plus DOC. PFS, or progression-free survival, was the main outcome. The objective response rate (ORR), disease control rate (DCR), overall survival (OS), and adverse event incidence were secondary objectives. Serum cytokine levels were assessed at the beginning of treatment in an exploratory investigation.

Results: Between April 2020 and June 2022, a total of 44 patients from 10 Japanese institutions were enrolled. The median OS was 22.6 months, whereas the median PFS was 6.3 months. Additionally, the DCR was 72.7% and the ORR was 36.4%. The PFS and OS were noticeably worse in the group with elevated vascular endothelial growth factor D (VEGF-D). A prolonged PFS was linked to both low and high levels of VEGF-D and VEGF-A.

Conclusion: our findings suggested that RAM with DOC following combination chemoimmunotherapy could be a practical and successful second-line treatment for patients with advanced non-small cell lung cancer in the real world.

Keywords : Ramucirumab, Docetaxel, Non-small-cell lung carcinoma, Combined drug therapy, VEGF-A, VEGF-D.

INTRODUCTION

The most common cause of cancer-related deaths nowadays is lung cancer. One The therapy prognosis for advanced lung cancer has significantly improved after the clinical discovery of immune checkpoint inhibitors (ICIs). 2-4 Furthermore, platinum-based chemotherapy has lately been replaced by innovative combination therapies, such as combined chemo-immunotherapy, as the standard of care for patients with advanced non-small-cell lung cancer (NSCLC). 5-7 However, there are significant clinical problems with the available therapeutic options following combined chemoimmunotherapy. A human recombinant IgG1 monoclonal antibody called Ramucirumab (RAM) targets the vascular endothelial growth factor (VEGF) receptor-2.8 in particular. In patients with advanced non-small cell lung cancer (NSCLC) who suffered disease progression following platinum-based chemotherapy, the efficacy of RAM plus docetaxel (DOC) combination

therapy was compared with that of DOC mono-therapy in the REVEL phase III clinical study. Several nations, including the US and Japan, have approved RAM with DOC, which is regarded as one of the common second-line therapies for advanced non-small cell lung cancer. Through inhibiting dendritic cell maturation and reducing the quantity of CD4 + and CD8 + T cells, VEGF modifies the tumour immune microenvironment. 10, 11 As an alternative, anti-angiogenic medications change the tumour milieu's immunosuppressive microenvironment to one that is immune permissive.

Combining anti-angiogenic medicines with ICIs has been shown in numerous clinical trials to increase anticancer activity against a variety of cancer types. 10. Due to its synergy as a combined therapy of anti-angiogenic agents and ICIs, atezozumab is useful in the treatment of non-small cell lung cancer (NSCLC), including epidermal growth factor receptor (EGFR)-positive lung cancer and liver metastases, when added to a combination of anti-VEGF antibody bevacizumab and chemotherapy. 6. According to earlier research, consecutive RAM plus DOC following ICI treatment is more beneficial than nonconsecutive RAM plus DOC following ICIs. 12–15 The pharmacodynamic effects of programmed cell death protein 1 (PD-1) receptor occupancy were considerably longer, lasting 85 days, and the measured half-life of anti-programmed cell death ligand 1 (PD-L1) antibody nivolumab has been reported to be 12–20 days. 16 Thus, following ICI treatment, a pseudo-combined impact of PD-1 blockage by RAM plus DOC and anti-angiogenic drugs may be anticipated. Evaluating RAM plus DOC's effectiveness following combination chemotherapy is essential since it has become the accepted first-line treatment for advanced non-small cell lung cancer. Furthermore, there are currently no potential predictive indicators for determining which NSCLC patients will benefit most from RAM treatment. This study examined the effectiveness, tolerability, and predictive biomarkers of RAM plus DOC as a second-line treatment following combination chemotherapy and immunotherapy in a real-world context in order to address these concerns.

MATERIALS AND PROCEDURES

Patients with advanced or recurrent non-small cell lung cancer (NSCLC) who gave written informed consent and received combination chemotherapy were prospectively included. The following were the requirements for inclusion: (i) unresectable advanced or recurrent NSCLC that has been proven by histology and cytology, and (ii) has undergone prior combination chemo-immunotherapy treatment. Individuals who had previously had systemic chemotherapy or immunotherapy following combined chemoimmunotherapy were not included. Every patient was monitored from the beginning of treatment. The Vardhman Mahavir Medical College & Safdarjung Hospital Ethics Committee in Delhi authorized the study plan, which was carried out in compliance with the Declaration of Helsinki's principles. The University Medical Hospital Information Network (VMMCS) Clinical Trials Registry (VMMCS243154) has the study protocol recorded. Prior to enrollment, written informed consent was given by each patient.

Evaluations of Soluble PD-L1, Serum VEGF-A, and VEGF-D

At the beginning of DOC plus RAM, blood serum samples were taken from every participant and kept at -80 °C. Human VEGF-A or VEGF-D enzyme-linked immunosorbent assay (ELISA) kits (RayBiotech, Inc., Norcross, GA, USA) were used to measure the serum concentrations of VEGF-A and VEGF-D. An ELISA kit (RayBiotech, Inc.) for Human/Cynomolgus Monkey PD-L1/B7-H1 was used to evaluate the serum concentrations of sPD-L1. For VEGF-A and VEGF-D, the median values served as the baseline cutoff values. In accordance with earlier research, we established the sPD-L1 cutoff value at 90 pg/mL. 17 Calculating the Sample Size The median PFS in the REVEL trial was 4.5 months (95% CI: 4.2-5.4 months). 9. In many retrospective investigations, the median PFS for chemotherapeutic pre-treatment alone (ICI naïve) was 3.8, 2.6, 4.1, and 2.3 months, while the median PFS for ICI pre-treatment followed by RAM plus DOC (ICI pre-treatment) was 5.1, 5.9, 5.7, and 5.7 months.12,15. With a significance level and power of 5% (2-sided) and 80%, respectively, the PFS for RAM plus DOC after combined chemotherapy and immunotherapy and RAM plus DOC with chemotherapy pre-treatment alone were assumed to be 6.0 and 3.0 months, respectively, based on these assumed PFS values and taking into account real-world data, including patients who were ineligible for clinical trials, such as patients with poor performance status (PS) and central nervous system metastases. This meant that 44 patients were needed.

Analysis of Statistics

The log-rank test was used to assess the differences between PFS and OS, which were determined using the Kaplan-Meier technique. When the lower limit of 95% confidence interval (CI) was over the threshold of PFS at 3.0 months, PFS was con- sided statistically substantially superior to the threshold value. Using the prevalent cause for stopping combined chemoimmunotherapy (86.4%; Table 1), the ORR values were displayed with 95% Cis using the the Wilson approach. The Common Terminology Criteria for Adverse occurrences version 5.0 grade was used to summarize adverse occurrences (AEs) in terms of safety. Hazard ratios (HRs) and 95% CIs were calculated for univariate analysis using Cox proportional hazards models; OS and PFS were centered on the date of last survival confirmation for patients who were

alive and had no recorded disease progression. The Eastern Cooperative Oncology Group performance status (ECOG-PS; ≥2), age (≥75 years), and sex were chosen as factors based on prior reports. 18 EZR statistics software version 1.40.19 was used to conduct statistical analysis.

RESULTS

Features of the Patient

In this study, 44 patients were recruited from 8 Japanese institutions between April 2020 and June 2022. A gastrointestinal hemorrhage prevented one patient from receiving RAM (Fig. 1). Thirty (68.2%) of the patients were male, thirty-four (77.3%) had a history of smoking, and the majority (93.2%) had an ECOG-PS of 0 or 1. The median (range) age was 69 (39-79) years. Adenocarcinoma (n = 31; 70.5%) and squamous cell carcinoma (n = 8; 18.2%) were among the histopathological subgroups. Nine patients (20.5%), nineteen (43.2%), and sixteen (36.4%) had PD-L1 tumor proportion scores of > 50%, 1%–49%, and less than 1%, respectively. None of the patients had anaplastic lymphoma kinase fusion, and six (13.6%) had EGFR mutations. Five patients received EGFR-TKI treatment prior to combination chemoimmunotherapy, with the exception of one who had EGFR exon20ins. The median interval between the initiation of RAM plus DOC and the final dosage of combination chemoimmunotherapy was 32.5 (14-505) days. Prior combination chemoimmunotherapy had a median PFS of 8.0 months (95% CI: 6.2-9.7). The most frequent cause of stopping combination chemoimmunotherapy was disease progression (86.4%; Table 1).

The effectiveness of RAM Plus DOC Following Combined Chemotherapy

13.9 months was the median follow-up period. Of the 44 lung cancer patients, 18 passed away before the deadline, and 35 saw disease progression. 6.3 months was the median PFS (95% CI: 4.2-8.8). The primary endpoint was met by this treatment protocol since it exceeded the threshold value (≥3.0 months of the lower limit value of the 95% CIs) (Fig. 2A). According to Fig. 2B, the median OS was 22.6 months (95% CI: 13.9-NE). The illness control rate was 72.7% (95% CI: 57.2-85.0) and the ORR was 36.4% (95% CI: 22.4-52.2). Overall, 16 patients (36.4%), 16 patients (36.4%), 8 patients (18.2%), and 4 patients (9.1%) had partial response, stable disease, progressing disease, and not assessable responses, respectively; no patients showed full response (0.0%; Supplementary Table S1). Similar efficacy was also demonstrated by the study that excluded patients with EGFR-positive lung cancer, with PFS and OS of 6.6 (95% CI: 4.2-10.2) and 22.2 (95% CI: 12.7-NE) months, respectively (Supplementary Fig. S1).

Impact of Serum Biomarkers on RAM Plus DOC Clinical Results

Then, as an exploratory research, we looked into how blood VEGF-A, VEGF-D, and sPD-L1 levels affected the results of RAM plus DOC combination therapy. Serum VEGF-A, VEGF-D, and sPD-L1 levels were assessed in 39 of the 44 recruited patients at the start of DOC plus RAM treatment (Fig. 1). The corresponding median (range) levels of VEGF-A, VEGF-D, and sPD-L1 were 161 (14-710), 968 (194-2571), and 65 (37-2587) pg/mL. The PFS and OS of the VEGF-D high group (n = 19) were substantially shorter than those of the VEGF-D low group (n = 20; Fig. 3) in terms of serum cytokines (4.5 vs. 6.3 months; P =.04, 15.5 vs. 30.1 months; P =.002, respectively).

Regarding PFS and OS, there were no discernible variations in serum levels of VEGF-A or sPD-L1. According to Supplementary Table S2, the ORR was substantially greater in the VEGF-A high group than in the VEGF-A low group (47.4% [95% CI: 24.4%–71.1%] vs. 15.0% [95% CI: 3.2–37.9%], P =.04). High VEGF-D levels were significantly associated with shorter PFS and OS in the univariate analysis (HR, 2.17, 95% CI: 1.02-4.62, P =.04; and HR, 4.94, 95% CI: 1.60-15.3, P =.005, respectively). High VEGF-D levels were found to be independently associated with reduced OS and PFS in the multivariate analysis (HR, 2.64, 95% CI: 1.15-6.03, P =.02; and HR, 7.25, 95% CI: 1.95-26.9, P =.003; respectively; Table 2).

We also examined the connection between patient characteristics and VEGF-D levels. Compared to the low VEGF-D group, the high VEGF-D group saw a significantly greater incidence of high VEGF-A levels (P =.03; Supplementary Table S3). There was a positive correlation between VEGF-D and VEGF-A levels (r = 0.41, P =.01; Supplementary Fig. S2). The predictive significance of the combination of VEGF-A and VEGF-D levels was further assessed. PFS was significantly longer for patients in the high VEGF-A + low VEGF-D group than for those in the other groups (high VEGF-A + low VEGF-D vs. low VEGF-A + high VEGF-D: P =.01; high VEGF-A + low VEGF-D vs. low VEGF-A + low VEGF-D: P =.04, high VEGF-A + low VEGF-D vs. high VEGF-A + high VEGF-D: P =.006; Fig. 4). According to these findings, a combination of pre-treatment serum levels of VEGF-A and VEGF-D may be a predictor of RAM plus DOC therapy responders.

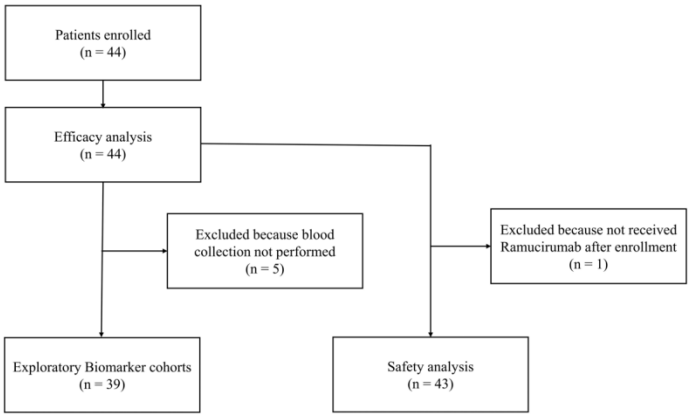


Figure 1 : It shows the study's CONSORT diagram. Consolidated Standards of Reporting Trials, or CONSORT.

Safety

Forty-three individuals who received at least one dosage of RAM with DOC underwent a safety analysis (Fig. 1). 38

Characteristics	All patients (*n* = 44)
Age	
Median (range)	69 (39-79)
Sex	
Male	30 (68.2%)
Female	14 (31.8%)
ECOG-performance status	
0	17 (38.6%)
1	24 (54.6%)
2	3 (6.8%)
Stage	
III/IV	41 (93.2%)
Recurrence	3 (6.8%)
Oncogenic driver	
EGFR mutation positivity	6 (13.6%)
ALK rearranged positivity	0 (0.0%)
Smoking status	
Current/former	34 (77.3%)
Never	10 (22.7%)
Histology	
Adeno	31 (70.5%)
Squamous	8 (18.2%)
Others	5 (11.4%)
PD-L1 status	
<1%	16 (36.4%)
1-49%	19 (43.2%)
≥50%	9 (20.5%)
Metastasis sites	
Brain	13 (19.6%)
Liver	3 (6.8%)
Bone	15 (34.1%)
Interval from combined chemoimmunotherapy to RAM + DOC, days	
Median (range)	32.5 (14-505)
Previous combined chemoimmunotherapy regimen	
Platinum + pemetrexed + pembrolizumab	22 (50.0%)
Platinum + paclitaxel/nab-paclitaxel + pembrolizumab	8 (18.2%)
Platinum + paclitaxel/pemetrexed + bevacizumab + atezolizumab	9 (20.5%)
Platinum + pemetrexed + atezolizumab	2 (4.5%)
Platinum + paclitaxel/nab-paclitaxel + atezolizumab	1 (2.3%)
Platinum + pemetrexed + ipilimumab + nivolumab	2 (4.5%)
Reasons for discontinuation of combined chemoimmunotherapy	
Due to progression disease	38 (86.4%)
Due to adverse event	6 (13.6%)

patients (88.4%) had all AE grades, while 18 patients (41.9%) had ratings ≥ 3. Eight patients (18.6%) had grade ≥ 3 neutropenia, while two patients (4.7%) had febrile neutropenia. Four (9.3%) and three (7.0%) patients, respectively, had all grades and grades ≥ 3 pneumonitis. There were no grade 5 AEs found (Table 3).

Table 1 : Patient Characteristics

DISCUSSION

For patients with non-small cell lung cancer (NSCLC), this prospective observational study showed that combined chemoimunotherapy with RAM + DOC was effective. Additionally, RAM plus DOC met the main objective with a PFS of 6.3 months (95% CI: 4.2-8.8) following combined chemoimmunotherapy. Following combination chemoimmunotherapy, the ORR for RAM plus DOC was 36.4% (95% CI: 22.4-52.2). Similar outcomes were shown in a recently published multi-center phase II prospective research on RAM + DOC following combined immunotherapy, with PFS and ORR of 6.5 months and 34.4%, respectively. 20 With PFS and ORR of 4.5 months and 22.9%, and 5.22 months and 28.9%, respectively, these outcomes were deemed superior to those of the REVEL trial and the phase II investigation of RAM + DOC in Japanese patients,9,21 indicating that the high effectiveness of RAM + DOC following combination immunotherapy is based on the synergistic effects of RAM and the history of ICIs prior to administration. In contrast to our findings, a prior retrospective trial that assessed RAM with DOC right after PD-1 blockade plus platinum-based chemotherapy found a median PFS and ORR of 4.1 months and 28.8%, respectively. 18.

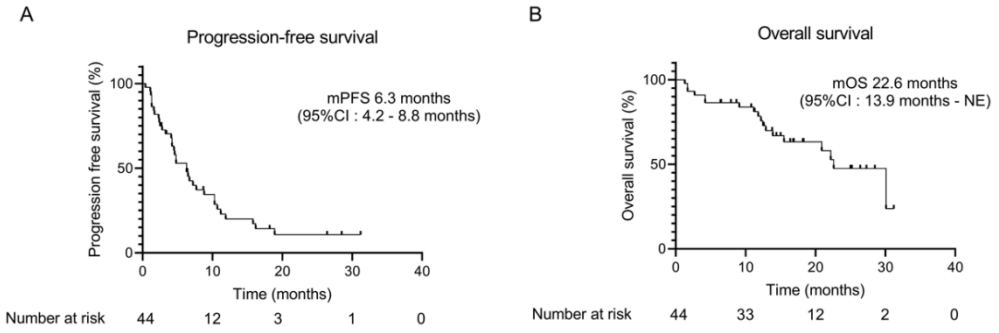


Figure 2: Following combination chemotherapy, displays the overall survival (OS) (B) and progression-free survival (A) of patients treated with docetaxel (DOC) and ramucirumab (RAM).

The inclusion of numerous susceptible patients with low PS may be one reason for this outcome. Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) levels and interstitial pneumonia were higher for grades ≥ 3 (7.0% and 2.3%, respectively) in the safety assessment than those that were reported to have happened in a RAM plus DOC prospective trial (2.6% and 1.3%, respectively). Consistent with the results of this trial, a retrospective analysis of RAM plus DOC following combination chemoimmunotherapy revealed that AST/ALT levels rose for grades ≥ 3 in 3.1% of patients and pneumonitis in 4.9% of cases, respectively. 18

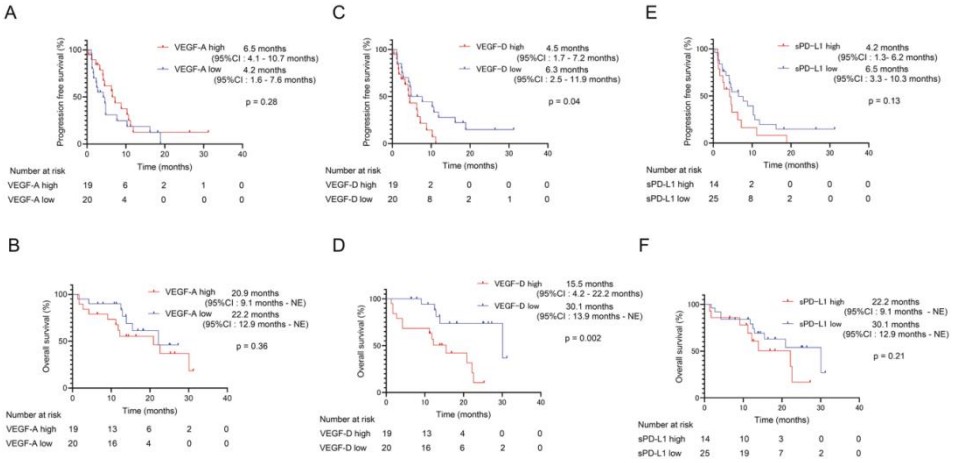


Figure 3: Overall survival (OS) and progression-free survival (PFS) according to blood levels of soluble programmed cell death ligand 1 (sPD-L1), VEGF-A, and VEGF-D. VEGF-A, VEGF-D, and sPD-L1 levels were stratified in order to

conduct PFS and OS analyses. PFS and OS Kaplan-Meier curves for patients with VEGF-A (A, B), VEGF-D (C, D), and sPD-L1 (E, F) are compared.

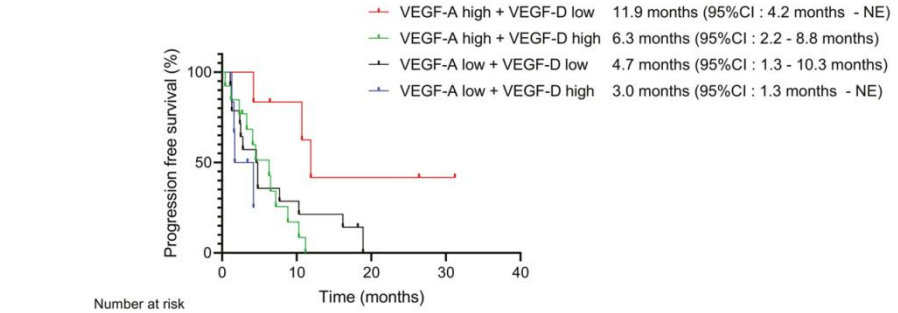
Increased AST/ALT levels and increased interstitial pneumonia could result from immune-related adverse events that take longer to manifest because of prior combination chemotherapy and immunotherapy. Patients treated with RAM plus DOC following ICI experienced greater adverse events (AEs), specifically peripheral neuropathy, fever, myalgia, arthritis, pleural effusions, pneumonia, and diarrhea, than those treated with RAM plus DOC ICI naïve, according to earlier retrospective investigations. 13. As a result, in a real-world environment, it might be required to be cautious about adverse events (AEs) such pneumonitis linked to the combination of DOC and RAM, especially in patients who have previously had ICI treatment. It is necessary to conduct more extensive research on the safety of this strategy. All things considered, these outcomes and our research suggest that RAM with DOC could be a useful and reasonably practical second-line treatment for patients with advanced non-small cell lung cancer who have received combination chemotherapy and immunotherapy. The most important element in the stimulation of neovascularization is the VEGF protein family. Furthermore, VEGF has been found to be a prognostic factor for a number of cancer types. Significant angiogenesis is induced by VEGF-A and its receptor, VEGFR2. By attaching itself to VEGFR2 and VEGFR3.8, VEGF-D promotes tumor angiogenesis and lymphangiogenesis. A poor prognosis is linked to elevated levels of VEGF-A and VEGF-D in cases of ovarian, breast, colorectal, and lung malignancies. 22–25.

Items	Progression-free survival		Overall survival	
(comparator)	Univariate	Multivariate	Univariate	Multivariate
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)
	P-value	*P*-value	*P*-value	*P*-value
VEGF-A high	0.68 (0.34-1.37)		1.57 (0.59-4.16)	
(vs. VEGF-A low)	*P* = .28		*P* = .36	
VEGF-D high	2.17 (1.02-4.62)	2.64 (1.15-6.03)	4.94 (1.60-15.3)	7.25 (1.95-26.9)
(vs. VEGF-D low)	*P* = .04	*P* = .02	*P* = .005	*P* = .003
sPD-L1 high	1.72 (0.84-3.50)		1.83 (0.71-4.77)	
(vs. sPD-L1 low)	*P* = .14		*P* = .21	
Age ≥ 75	0.34 (0.05-2.51)	0.21 (0.03-1.63)	5.03 (0.99–25.3)	4.69 (0.88-24.8)
(vs. < 75)	*P* = .29	*P* = .14	*P* = .05	*P* = .07
Male sex	1.37 (0.62-3.01)	1.53 (0.64-3.70)	1.10 (0.40-3.06)	0.50 (0.15-1.63)
(vs. female sex)	*P* = .43	*P* = .34	*P* = .85	*P* = .25
ECOG-PS 2	1.38 (0.32-5.89)	2.50 (0.49-12.8)	1.58 (0.32-7.90)	2.61 (0.41-16.7)
(vs. 0,1)	*P* = .66	*P* = .27	*P* = .58	*P* = .31
Smoker	1.01 (0.41-2.48)		0.62 (0.20-1.92)	
(vs. never smoker)	*P* = .99		*P* = .41	
Adeno	0.72 (0.30-1.73)		1.10 (0.31-3.84)	
vs. non-Adeno	*P* = .47		*P* = .88	
PD-L1 ≥ 50%	0.54 (0.19-1.56)		0.31 (0.04-2.32)	
(vs. < 50%)	*P* = .26		*P* = .25	
EGFR mutation positive	1.56 (0.59-4.12)		0.86 (0.20-3.75)	
(vs. all others)	*P* = .37		*P* = .83	
Liver metastasis	2.77 (0.63-12.2)		2.78 (0.33-23.1)	
(vs. non liver metastasis)	*P* = .18		*P* = .34	
Brain metastasis	1.09 (0.50-2.37)		1.01 (0.32-3.13)	
(vs. non brain metastasis)	*P* = .84		*P* = .99	
Bone metastasis	1.50 (0.73-3.01)		1.02 (0.38-2.77)	
(vs. non bone metastasis)	*P* = .37		*P* = .96	
Bevacizumab administration	1.49 (0.64-3.48)		1.24 (0.40-3.80)	
(vs. non Bevacizumab administration)	*P* = .36		*P* = .71	
Interval from combined chemoimmunotherapy to RAM + DOC ≥ 60 days	1.98 (0.83-4.69)		0.73 (0.21-2.56)	
(vs. < 60 days)	*P* = .12		*P* = .62	
PFS of combined chemoimmunotherapy > 8.8 months	0.58 (0.28–1.17)		0.59 (0.23-1.53)	
(vs. < 8.8 months)	*P* = .13		*P* = .28	
discontinuation of combined chemoimmunotherapy due to progression disease	1.14 (0.40-3.29)		2.70 (0.36-20.5)	
(vs. due to adverse event)	*P* = .80		*P* = .34	

Table 2 : Cox hazard models, both univariate and multivariate, for RAM + DOC overall survival and progression-free survival.

Moreover, a number of blood cytokines have been shown to be strong indicators of angiogenesis inhibitors, or ICIs. 26, 27 In metastatic duodenal and jejunal adenocarcinomas of breast cancer, serum VEGF-A levels have been identified as indicators of bevacizumab efficacy. 28, 29 High plasma VEGF-D levels were linked to better PFS and OS in patients with colorectal cancer treated with RAM + FOLFIRI, according to the RAISE research assessing the disease. 30. Nevertheless, there are currently no predictive biomarkers available to identify NSCLC patients who stand to gain more

from treatments that contain RAM. In order to find possible RAM biomarkers, this study assessed baseline serum VEGF-A and VEGF-D levels. Additionally assessed was the serum-soluble version of PD-L1 (sPD-L1), which binds to PD-1 receptors and may be crucial for immuno-regulation17. To the best of our knowledge, this is the first prospective real-world study to evaluate pre-treatment biomarkers of RAM plus DOC in patients. Given their potential to become the foundation of customized medicine in the future, biomarkers that can predict treatment results are essential. NSCLC following combination chemoimmunotherapy treatment. Consequently, given their potential to serve as the foundation for customized medicine in the future, clinical research initiatives focused on finding biomarkers that may forecast



Number at risk					
VEGF-A high + VEGF-D low	6	4	2	1	0
VEGF-A high + VEGF-D high	13	2	0	0	0
VEGF-A low + VEGF-D low	14	4	2	1	0
VEGF-A low + VEGF-D high	6	0	0	0	0

treatment results are essential.

Figure 4 : It displays how the ratio of VEGF-A to VEGF-D affects progression-free survival (PFS).

High VEGF-A and low VEGF-D levels together acted as a prognostic indicator of RAM plus DOC's effectiveness in this investigation. Interestingly, VEGF-A had a positive correlation with RAM plus DOC efficacy but VEGF-D had a negative correlation, even though VEGF-A and VEGF-D levels were favorably associated. The distinct binding receptors of VEGF-A and VEGF-D could be the cause of this disparity. VEGF-A primarily binds to VEGFR2, promoting angiogenesis; in contrast, VEGF-D binds to both VEGFR2 and VEGFR3, exhibiting different tumor-promoting effects,

	All grade		Grade 3 or higher	
	Number of cases	%	Number of cases	%
N	43			
All adverse events	38	88.4	18	41.9
Neutropenia	13	30.2	8	18.6
Stomatitis	5	11.6	0	0.0
Thrombocytopenia	5	11.6	0	0.0
Interstitial lung disease	4	9.3	3	7.0
Leg edema	4	9.3	0	0.0
Paronychia	3	4.7	1	2.3
Febrile neutropenia	2	4.7	2	4.7
Intracranial hemorrhage	2	4.7	2	4.7
AST ALT increased	2	4.7	1	2.3
Hypertension	2	4.7	0	0.0
Nausea	2	4.7	0	0.0
Proteinuria	2	4.7	0	0.0
Dysgeusia	2	4.7	0	0.0
Alopecia	2	4.7	0	0.0
Peripheral neuropathy	2	4.7	0	0.0
Pneumothorax	1	2.3	1	2.3
General edema	1	2.3	1	2.3
Hyponatraemia	1	2.3	1	2.3
Fracture	1	2.3	1	2.3
Anorexia	1	2.3	1	2.3
Malaise	1	2.3	1	2.3
Gastrointestinal hemorrhage	1	2.3	1	2.3
Epistaxis	1	2.3	0	0.0
Anaemia	1	2.3	0	0.0
Bloody stools	1	2.3	0	0.0
Constipation	1	2.3	0	0.0
Dyspnoea	1	2.3	0	0.0

such as tumor development, angiogenesis, lymphangiogenesis, metastasis, and immunosuppression. 31.

Table 3 : Safety Evaluation

Additionally, it has been found that VEGF-D has a greater affinity for VEGFR3 than for VEGFR2.32. VEGF-D may contribute to a poor prognosis, mostly by binding to VEGFR3 and causing lymphangiogenesis and immunosuppression, even while RAM inhibits VEGFR-2 signaling that is stimulated by both VEGF-A and VEGF-D. These results run counter to the RAISE trial's findings, which may have been impacted by the fact that bevacizumab was administered as a first-line treatment to every patient in that research. Therefore, more research is required to confirm these theories and ascertain how VEGF-A and VEGF-D affect the effectiveness of angiogenesis inhibitors in advanced non-small cell lung cancer. There are several restrictions on this study. The sample size was small, to start. Second, only other patients were included. Third, there was not enough time to evaluate the OS data because the follow-up period was so brief. Fourth, the biomarker analyses were conducted as preliminary research. Additional prospective research is necessary to corroborate these findings because some of the analyses, such as univariate and multivariate analyses, were conducted retrospectively. Lastly, as only NSCLC patients received DOC plus RAM following first-line chemotherapy, there may have been a selection bias.

CONCLUSION

Our prospective trial showed that, in the real world, RAM + DOC combined therapy may be a helpful and generally safe second-line treatment for advanced non-small cell lung cancer following combined chemoimmunotherapy. One potential biomarker for predicting the effectiveness of RAM with DOC is the combination of serum VEGF-A and VEGF-D.

Conflict of Interests

None

Ethics Approval

The Vardhman Mahavir Medical College & Safdarjung Hospital Delhi Ethics Committee accepted the study protocol, which was carried out in compliance with the Declaration of Helsinki's principles. Prior to enrollment, written informed consent was given by each patient.

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